The Investigation and Treatment of Diabetic Gastroparesis

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ABSTRACT

Purpose: This review provides an update on the investigations and treatment options for gastroparesis.

Methods: A comprehensive literature search of Medline, PubMed, Embase and OVID was conducted which included all systematic reviews and research articles that focused on the diagnosis, investigations and management diabetic gastroparesis.

Findings: Dietary modifications and pharmacologic treatment with prokinetics to increase gastric motility form the mainstay of treatment. However, the use of prokinetics is limited by adverse effects and serious adverse effects, leaving metoclopramide as the only drug approved by the US Food and Drug Administration for the treatment of gastroparesis. Newer therapies, including motilin receptor agonists, ghrelin receptor agonists, and neurokinin receptor antagonists, are currently being investigated. Transpyloric stenting, gastric electrical stimulation, and gastric per-oral endoscopic myotomy provide mechanical options for intervention, and surgical interventions in severe intractable gastroparesis include laparoscopic pyloroplasty or gastrectomy.

Implications: Advances to better understand the pathophysiology and management of diabetic gastroparesis have been limited, especially with discordance between symptoms and severity of delay in gastric emptying. Established treatment options are limited; however, recent pharmacologic and surgical interventions show promise. (*Clin Ther*. 2018;▮:▮▮▮–▮▮▮) © 2018 Elsevier HS Journals, Inc. All rights reserved.

Key words: Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus, Gastroparesis, Microvascular.

INTRODUCTION

First described by Rundles in 1945,[1] the term *gastroparesis diabeticorum* was coined by Kassander in 1958.[2] The most common cause of gastroparesis, a condition characterized by delayed gastric emptying in the absence of a mechanical obstruction, is diabetes mellitus.[3,4] This condition can manifest in a variety of symptoms, including early satiety, nausea, vomiting, and anorexia. It can be associated with significant morbidity and impaired quality of life, with anxiety and depression and an effect on patients' self-management of diabetes, especially with fluctuating glucose levels.[5,6] However, the association between the severity of symptoms and delay in gastric emptying is not linear.[7] Indeed, up to 40% of patients with

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diabetic gastroparesis (DG) can be asymptomatic.[8] The term *gastric hypoglycemia* has been used to describe patients with hypoglycemia attributable to gastroparesis, and it should be considered in the differential diagnosis for patients diagnosed as having brittle diabetes.[9,10] A comprehensive literature search of Medline, PubMed, Embase and OVID was conducted which included all systematic reviews and research articles that focused on the diagnosis, investigations and management of diabetic gastroparesis.

EPIDEMIOLOGY

The exact prevalence of DG remains unknown. A major population-based study, evaluating symptoms, reported a 10-year cumulative incidence of gastroparesis of 5.2% in patients with type 1 diabetes mellitus (T1DM), 1.0% in patients with type 2 diabetes mellitus (T2DM), and 0.2% in controls.[11] The T1DM Exchange registry data reported 4.8% of patients had gastroparesis, with significant associations with female sex, longer duration of diabetes, older age, and more frequent severe hypoglycemic episodes, despite higher glycosylated hemoglobin (HbA_{1c}) levels.[12] Although less common than in patients with T1DM, the greater prevalence of T2DM means that more patients have gastroparesis attributable to this condition.[8] There are conflicting data on the prevalence of symptoms of gastroparesis in patients with diabetes.[13,14] In addition to delayed gastric emptying, patients may also develop rapid gastric emptying, with one study reporting this phenomenon in 22% of patients evaluated with scintigraphy.[15]

An interesting phenomenon is that of symptom turnover (the appearance and disappearance of symptoms over time), and several studies found this to be common in patients with DG. One study remarked that the turnover of symptoms was associated with depression rather than other factors, such as glycemic control.[16,17]

PATHOPHYSIOLOGY

The effective movement of gastric contents through the stomach depends on 2 major activities: peristalsis of gastric smooth muscle propelling contents to the pylorus and dilation of the pyloric sphincter. Interstitial cells of Cajal (ICCs) are specialized pacemaker cells that drive the contraction of gastric smooth muscle. The speed, strength, and, to a lesser degree, frequency of these contractions are known to be modified by both neurologic and neuroendocrine modulation.

Gastroparesis is defined as the delayed removal of stomach contents in the absence of a physical obstruction.[18] Hyperglycemia mediates nerve damage through a wide range of mechanisms, including poly–adenosine triphosphate ribose, advanced glycosylation end (AGE) products, endoplasmic reticulum stress, oxidative stress, inflammation, and ischemia,[19,20] which result in demyelination and axonal degeneration.[21,22] Neuropathy, affecting autonomic input, such as from the vagus nerve, or that affecting the enteric nervous system's own intrinsic neurons, can induce gastroparesis. Loss of parasympathetic stimulation will slow gastric emptying, a picture mimicked during surgical vagotomy.[23] Extensive myelinated and unmyelinated nerve fiber and endoneurial capillary pathologic findings have been found in the vagus nerve of diabetic patients with severe gastroparesis, although interestingly this was comparable to 2 diabetic patients without gastroparesis.[24] Both direct neurologic feedback from the small bowel and hormones, such as cholecystokinin and gastric inhibitory peptide, can limit the flow of chyme into the duodenum. Abnormalities of gastric electrical rhythm and transmission can lead to a disruption of the migrating motor complex, ineffective propulsion, and decreased pyloric output.[25,26] The severity of these arrhythmias has been directly linked to loss of ICCs, although not to the severity of symptoms.[27] The origin of gastroparesis has therefore been related to the pathologic features of the ICCs and vagal neurons.[28,29]

Neural nitric oxide synthase (nNOS) expressed in gastric neurons induces relaxation and accommodation, although its predominant function is to cause dilatation of gastrointestinal sphincters, including the pylorus.[29] In animal models of DG, reduced nNOS mRNA, protein, and function[30] restricts the passage of food into the duodenum. Interestingly, the reduction in nNOS is not attributable to a loss of active neurons but decreased expression on these intrinsic neurons.[8]

A significant decrease in ICC counts has been found in gastric biopsy specimens of patients with gastroparesis.[31–34] Interestingly, biopsy specimens of patients with gastroparesis-like syndrome (no evidence of delayed gastric emptying) reveal significantly lower ICC counts,[35] emphasizing their critical importance to gastroparesis. Indeed, a decreased ICC count is a key histologic finding in gastroparesis.[29] Unlike diabetic neuropathy where the deleterious effects stem from

hyperglycemia, evidence suggests that the decrease in ICC counts is related to the body's response to this condition. Murine models indicate that hyperglycemia per se is not the cause of decreased ICC counts but rather a decrease in the quantity or sensitivity to insulin and insulin-like growth factor.[36,37]

Murine models using streptozotocin diabetes show a decrease in ICC density and a delay in gastric emptying.[38] However, when streptozotocin was given to mice that genetically lacked Csf1, a factor essential for the development of macrophages in gastrointestinal musculature, the effect on ICCs and emptying was lost,[39] suggesting a potential role for macrophage-mediated induction of DG. Gastric macrophages differentiate and are classed as M1, a proinflammatory phenotype, or M2, an anti-inflammatory phenotype.[40] Murine gastroparesis models relatively express larger populations of M1 compared with M2.[41] The presence of the M2 phenotype has been found to protect against gastroparesis in mice through a potent antioxidant, heme oxygenase 1–dependent process.[42] Up-regulation of heme oxygenase 1 by hemin, a process reproducible in humans, reverses the loss of ICCs, gastric motility, and nNOS in animal models of DG.[42] In patients with gastroparesis, a loss of $CD206^{+}$ macrophages of the M2 phenotype in the gastric antrum is related to the ICC density.[41] Recent studies show that insulin and insulin-like growth factor 1 can affect macrophage function by promoting inflammation,[43–45] which may explain how these factors contribute to ICC loss.

Pharmacologic management of diabetes may also affect gastric motility. Endogenous glucagon-like peptide 1 slows gastric emptying[46]; therefore, exogenous glucagon-like peptide 1 analogues and dipeptidyl peptidase 4 inhibitors could theoretically delay gastric emptying. However, clinical studies have not found any effect of these therapies on gastric emptying.[47–49]

INVESTIGATIONS

The diagnosis of gastroparesis entails the exclusion of a mechanical obstruction, typically with an oesophagogastroduodenoscopy or barium meal. The gold standard for diagnosis is scintigraphy, although breath testing and the SmartPill have been developed as alternatives. Other modalities, such as ultrasonography, magnetic resonance imaging, and electrogastrography, are much less commonly used.

Gastric-emptying scintigraphy

There has been an attempt to standardize test protocols using gastric-emptying scintigraphy.[50] A standard low-fat meal is used, although this can be combined with an isotope-labeled liquid. Although a delay in liquid emptying may not be apparent until the development of severe gastroparesis, the sensitivity for detecting gastroparesis may be improved if there is delayed liquid emptying in the presence of normal solid emptying.[51–53] After an overnight fast, a standard, low-fat, radiolabeled meal is ingested within 10 minutes, and imaging is performed at baseline and 1, 2, and 4 hours with the patient in a standing position. Glucose level should be <275 mg/dL, and use of drugs that affect gastric emptying needs to be discontinued before the procedure. Delayed gastric emptying is defined by $>60\%$ retention at 2 hours or $>10\%$ retention at 4 hours. A major consideration for this form of imaging is that females can have a physiologic delay in gastric emptying of approximately 15%. Additional pitfalls include intraindividual variation of gastric emptying of up to 24%, and the use of an abnormal low-fat, low-fiber meal that may not mimic real-life meals and thereby lower sensitivity.[54]

Gastric Emptying Breath Test

The gastric emptying breath test relies on the use of a radiolabeled carbon-containing test meal (carbon 13–labeled S platensis or octanoic acid). A similar preparation to gastric-emptying scintigraphy is needed for this investigation. The radiolabeled carbon is released during digestion, and the carbon dioxide is released by respiration through ventilation is measured 4 to 6 hours later. Any exertion that results in increased ventilation rate needs to be avoided.[54,55] This investigation may be as accurate as gastric-emptying scintigraphy.[56]

Wireless motility capsule

The SmartPill can evaluate pH, pressure, and temperature in addition to whole gut transit time. Data are transmitted directly to a portable receiver. The SmartPill is ingested with a standard meal after use of acid-suppressing medications have been discontinued. Movement of the capsule from an acidic to an alkaline environment represents transit from the stomach to the duodenum, normally within 5 hours. The use of this

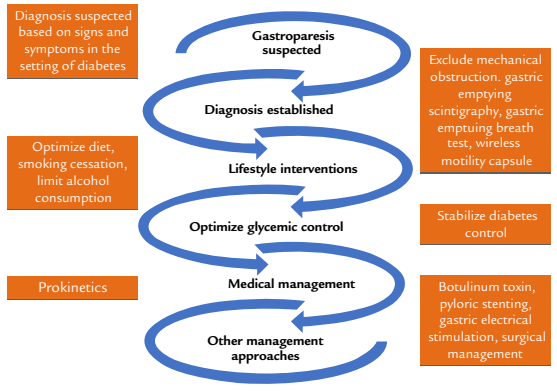

Figure. Approach to investigations and management.

diagnostic modality allows for ambulatory assessment of patients, is radiation free, and may also provide additional physiologic information.[54]

MANAGEMENT

The general principles of management are to restore nutritional and hydration status, alleviate symptoms, and stabilize diabetes control. The Figure shows an approach to investigations and management.

Dietary Modifications

In conjunction with improving nutrition, fluid and electrolyte balance also needs to be corrected. Correction of prolonged poor nutrition may predispose patients to refeeding syndrome. Multiple small meals (4 to 6 per day) are preferred to fewer large ones. Meals should be low in fat and fiber because these can slow gastric emptying.[57–59] Smoking and alcohol consumption may also delay gastric emptying and should be avoided.[60,61] A trial of 56 patients with DG found that a small particle size diet may alleviate symptoms.[62] High-calorie liquid drinks may also be a useful adjunct to the management of gastroparesis. Certain foods, such as pizza, orange juice, coffee, broccoli, salsa, and roast beef, which fall into the categories of spicy, acidic, fatty, and high fiber and may delay gastric emptying, should be limited or excluded.[63]

When oral nutrition is not possible or inadequate, assisted nutrition should be considered. The enteral route is preferable to parenteral nutrition when possible because of the lower risk of complications, such as line infection and thrombosis. A nasojejunal tube may be used initially, followed by a jejunostomy tube, if required.[59]

Glycemic control

The association between glycemic control and gastroparesis is not fully understood and, of course, may be bidirectional. Earlier studies found that acute hyperglycemia delayed gastric emptying in healthy individuals.[64,65] Subsequent studies found that in people with T1DM, hyperglycemia prolonged gastric emptying of solids and liquids,[66–68] with reduced antral mobility and increased proximal gastric adherence.[67,69] In contrast, acute hypoglycemia accelerates gastric emptying in healthy controls.[70] Paradoxically, in patients with T2DM, a higher fasting blood glucose level was associated with faster gastric emptying.[71,72]

There are conflicting data on the effect of long-term glycemic control on gastric emptying, with several studies having previously found no correlation in patients with T2DM and T2DM.[71,73–75] However, recently, in a follow-up cohort of 78 patients from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications studies who underwent an assessment of gastric emptying using the breath test, baseline HbA_{1c} level, duration of diabetes, and mean HbA_{1c} level during the trial period were associated with delayed gastric emptying.[76] A further retrospective study of patients with diabetes who had undergone gastric-emptying scintigraphy found that a higher HbA_{1c} level was significantly associated with higher gastric retention at 4 hours.[77]

PHARMACOLOGIC TREATMENT

Prokinetics, used to promote gastrointestinal tract motility, have been and remain the mainstay of treatment for gastroparesis (Table).[78] However, data are lacking on the long-term effectiveness of these drugs, perhaps also reflecting the varying clinical course of this condition whereby long-term treatment is often not necessary.[7]

Metoclopramide

Metoclopramide is a potent dopamine D_2 receptor antagonist and serotonin (5HT4) receptor agonist that acts on the brainstem and peripheral nerves. In the

Table. Pharmacological treatment options for the management of diabetic gastroparesis.

Class of Medication	Effect on GI Tract	Use in Diabetic Gastroparesis
Dopamine D_2 receptor antagonists (metoclopramide, domperidone) approved for diabetic gastroparesis. Domperidone may avoid CNS adverse effects.	Increases contractions of the gastric antrum by releasing acetylcholine from enteric neurons	Metoclopramide is FDA
Motilin receptor agonists (erythromycin, mitemcinal, and camicinal)	Increased antral contraction	Erythromycin favored in extremely unwell, hospitalized patients, risk of tachyphylaxis with erythromycin
5HT4 receptor agonists (cisapride, tegaserod, revexepride)	Increased muscular contraction via cholinergic pathways	Older agents not used due to cardiac safety concerns, more selective agents undergoing evaluation
Ghrelin receptor agonists (TZP 101, TZP 102, relamorelin)	Increased migrating motor complexes (Phase III) and vagal signaling.	Significant improvement in symptoms in clinical trials
Neurokinin receptor antagonists (aprepitant)	Antiemetic, antagonizes the effects of substance P	Limited trial data

CNS = central nervous system; FDA = US Food and Drug Administration; GI = gastrointestinal.

gastrointestinal tract, it increases contractions of the gastric antrum by releasing acetylcholine from enteric neurons.[79–81] The central effects may account in some part for the reduction of nausea. An early double-blind, placebo-controlled trial of 40 patients with DG found that metoclopramide 10 mg QID PO produced a significant improvement in meal tolerance, symptoms of gastroparesis, and gastric emptying during 3 weeks.[82] In a subsequent double-blind, placebo-controlled study of 13 patients with DG, metoclopramide was administered parenterally and then orally before each meal and before bed and produced a mean symptom reduction of 52.6% and improved gastric emptying in 7 patients.[83] It remains the only drug approved by the US Food and Drug Administration (FDA) for the treatment of gastroparesis. However, concerns regarding potentially irreversible tardive dyskinesia has led to an FDA warning restricting its use to no longer than 3 months and recommendations to use the lowest effective dose for the shortest possible time. Indeed, along with older age and female sex, diabetes itself is a risk factor for developing tardive dyskinesia.[81]

Domperidone

Domperidone, another dopamine D_2 receptor antagonist, does not cross the blood brain barrier and therefore does not cause the same central nervous system adverse effects.[84] A dose of 10 mg TID improves a range of gastroparesis-related symptoms.[85] This drug is not currently FDA approved, and its prescription in the United States requires an investigational new drug application because of the risk of QTc prolongation and cardiac arrhythmias.

Motilin Receptor Agonists

Erythromycin is a macrolide antibiotic that agonizes motilin receptors, leading to increased antral contraction.[86] The intravenous route is strongly favored in hospitalized patients, although tachyphylaxis may occur with this drug usually after 4 weeks of use.[87] There are potential interactions with other drugs because of cytochrome P450 C3A4 inhibition. Clarithromycin and azithromycin have also been used, but there is a paucity of supporting clinical trial data. A retrospective case-control analysis

of 120 patients found equal efficacy between azithromycin and erythromycin in accelerating gastric emptying in gastroparesis.[88] A smaller study that evaluated intravenous use of erythromycin and azithromycin found similar stimulation of antral activity with a longer duration of effect.[89] The advantages of azithromycin are the lack of P450 inhibition, longer duration of action, and better adverse effect profile; however, more research needs to be performed to investigate its utility further. Macrolides can also cause QTc prolongation through their effect on I_{Kr} potassium channels.[90]

New agents acting on the motilin receptor, including mitemcinal and camicinal, deliver the benefits of treatment without the antibiotic activity reducing the risk of tachyphylaxis. However, a double-blind, placebo-controlled trial of mitemcinal found no symptom relief compared with placebo despite an improvement in gastric emptying.[91] A single dose of camicinal in patients with T1DM significantly accelerates gastric emptying of solids, and further trials are under way.[92]

5HT4 Receptor Agonists

The 5HT4 receptor agonist class of drugs activate 5HT4 receptors, leading to increased muscular contraction via cholinergic pathways.[93] Cisapride, a 5HT4 receptor agonist and established drug for gastroparesis, was withdrawn because of cardiac safety concerns attributable to activation of hERG potassium channels, leading to QTc prolongation and ventricular arrhythmias. Similarly, tegaserod, another 5HT4 agonist, has been withdrawn because of cardiac safety concerns.[94] Recently, more selective 5HT4 receptor agonists have been developed, but a trial of revexepride in patients with gastroparesis found no benefit on symptoms or gastric emptying versus placebo.[95]

Ghrelin Receptor Agonists

Ghrelin is a peptide released from gastric mucosal endocrine cells.[96] Stimulation of the GHS-R1a receptor results in increased migrating motor complexes (Phase III) and vagal signaling.[97,98] Four single daily intravenous infusions of TZP 101 (ulimorelin) were associated with a significant improvement in symptoms of gastroparesis up to 30 days after administration in 23 patients with DG compared with placebo.[99] In a Phase IIa trial of 92 patients with DG, TZP 102, an oral ghrelin receptor agonist, produced a significant improvement in symptoms during 28 days.[100] A subsequent Phase IIb study of TZP 102 in 201 patients with DG found significant symptom improvement but failed to establish efficacy compared with placebo.[101] Recently, relamorelin, a subcutaneously administered ghrelin agonist, also produced a significant improvement in vomiting and gastric emptying compared with placebo in patients with DG.[102]

Neurokinin Receptor Antagonists

Substance P is a peptide involved in the induction of vomiting, with actions through binding to neurokinin 1 receptors.[103] Aprepitant is an neurokinin 1 receptor antagonist that is currently widely used in chemotherapy-induced vomiting and nausea. Fountoulakis reported 2 cases of DG that were successfully treated with aprepitant for 12 and 18 months.[104] There are currently no published trials of this drug for DG.

OTHER THERAPIES

Botulinum Toxin

A manifestation of DG is pylorospasm, and botulinum toxin, which blocks acetylcholine release at the neuromuscular junction and reduces excessive pyloric contraction, has been evaluated.[105–107] Initial case series showed an improvement in symptoms and gastric emptying[108–110]; however, 2 small randomized controlled trials have not yielded positive results,[111,112] questioning the efficacy of this treatment in gastroparesis.[113] Furthermore, a retrospective analysis of 179 cases treated with botulinum toxin suggested that diabetes further limited a benefit.[114]

Transpyloric Stenting

Endoscopic stent placement has been investigated in small series of patients with gastroparesis. Khashab et al[115] reported their experience in 30 patients undergoing a total of 48 procedures. Although the data were incomplete, there were reports of symptom improvement and more rapid gastric emptying, but stent migration is a complication. The authors suggested that transpyloric stenting may be a useful salvage therapy or may help identify patients who may benefit from other therapies directed at the pylorus.

Gastric Electrical Stimulation

Gastric electrical stimulation treatment has been approved by the FDA and the National Institute for Health and Care Excellence for the treatment of drug refractory DG. A device implanted into the abdominal wall has leads that extend into the greater curvature of the stomach and generates 12 pulses per minute. Abell et al[116] studied 38 patients undergoing gastric electrical stimulation and found a reduction in symptoms with associated weight gain. Long-term follow-up has reported morbidity reduction for up to 10 years after the procedure.[116,117] Heckert et al[118] reported an improvement in symptoms in 75% of 151 patients undergoing this procedure, and patients with diabetes surprisingly had greater success.

Gastric Per-Oral Endoscopic Myotomy

Khashab et al[119] reported an improvement in symptoms in 26 of 30 patients undergoing gastric per-oral endoscopic myotomy for refractory gastroparesis. However, in patients undergoing this procedure for mechanical obstruction, there was a high rate of dumping syndrome with postprandial hypoglycemia, but this appears less common in patients with gastroparesis.[120]

SURGICAL TREATMENTS

A number of treatments have been used in severe intractable gastroparesis. Laparoscopic pyloroplasty was evaluated retrospectively in 46 patients and revealed a significant symptom improvement and gastric emptying in 90% of cases.[121] Gastrectomy has also been used in selected patients to alleviate severe refractory symptoms, may be considered in those with high risk of renal failure or premature death,[122–124] and may be considered earlier in patients with failed GES.[125] Pancreatic transplantation may be of benefit in DG, perhaps in the short term via improved glycemic control and in the long term through nerve fiber regeneration.[126,127]

APPROACH TO THE MANAGEMENT OF GASTROPARESIS

The American College of Gastroenterology guidelines recommend that a documented delay in gastric emptying is required for the diagnosis, with scintigraphy being the most reliable gold standard.[113] Other alternatives still require further validation for use in the diagnosis of DG. Before undertaking any investigation, use of all medications that have the potential to affect gastric emptying must be stopped for at least 48 hours. These medications include narcotic opioid analgesics and anticholinergic agents (may give a falsely delayed result) or the medications metoclopramide, domperidone, and erythromycin (which accelerate gastric emptying and may give a falsely normal result). Hyperglycemia can lead to a deterioration in symptoms, so glycemic control should be measured and improved before testing during any gastric emptying studies.

Primarily, the management of DG is ensuring hydration, adequate electrolytes, and nutritional support. One of the main themes of any guidelines on gastroparesis is the importance of optimizing glycemic control. Dietician input should be sought with regard to the consumption of frequent small-volume meals low in fat and soluble fiber. The guidelines suggest that indications for enteral nutrition include unintentional loss of ≥10% of usual weight during 3 to 6 months and/or repeated admission for refractory symptoms. A nasogastric tube should be used initially, followed by a jejunostomy if indicated. This approach may reduce hospital admissions and improve symptoms.[128]

The strongest evidence and recommendations are with metoclopramide as the first line of prokinetic therapy, which should be given at the lowest effective dose in liquid formation to facilitate absorption. It is approved for a duration of 12 weeks, and advice should be given to discontinue therapy if patients develop adverse effects, such as tardive dyskinesia. If patients do not tolerate metoclopramide, then domperidone can be used with investigational new drug clearance from the FDA. Domperidone does not have the predisposition for central nervous system adverse effects as metoclopramide does; however, there is a tendency for this to cause a prolonged QTc in interval, so a baseline ECG in recommended. If the QTc is >470 msec in men and 450 msec in women, then this should be withheld. A follow-up ECG while the patient is receiving domperidone treatment is advised. The use of erythromycin orally and intravenously in hospital when intravenous prokinetic therapy is initiated is recommended.

The surgical procedures mentioned earlier may be considered on an individual basis in refractory cases. In patients in whom nausea and vomiting are an issue,

antiemetics should be considered for symptomatic treatment, and in refractory cases, tricyclic antidepressants can be used; however, caution must be taken they may retard gastric emptying. The National Institute for Health and Care Excellence guidelines advise that gastric electrical stimulation is an option patients with chronic, intractable nausea and vomiting, and its use in particular is beneficial in DG.[129]

CONCLUSION

DG remains a challenging complication of diabetes. Advances in understanding the pathophysiology of this condition have been limited. The management of gastroparesis is difficult because there is discordance between symptoms and the degree of delayed gastric emptying. Because of the relatively low prevalence of DG and the fluctuating symptoms, it is often difficult to recruit patients into clinical trials. Current treatment options are limited; however, recent pharmacologic and endoscopic interventions show promise.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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